UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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JAN 2 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: 4-Amino-6-(1,1-dimethylethyl)-3-(methylthio) -1,2,4-triazin-5(4H)-one (DIC 1468 Technical or Metribuzin): Review of a study on dermal sensitization in guinea pigs submitted by the registrant.

Caswell No.: 033D
HED Project No.: 1-1528
MRID No.: 415551-01

FROM: Walter J. Kozumbo, Ph.D., Toxicologist 12-20-91
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Robert Taylor/Vickie Walters, PM Team 25
Registration Division (H7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head 12/20/91
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C) 12/20/91

REGISTRANT: MOBAY Corporation

ACTION REQUESTED: Review a skin sensitization study performed on guinea pigs with the herbicide Metribuzin according to FIFRA guideline 81-6.

1 of 6

CONCLUSIONS:

A copy of the study entitled **"DIC 1468 Technical (Metribuzin): STUDY OF SKIN SENSITIZATION EFFECT ON GUINEA PIGS (Buehler Test)"** has been received and reviewed by the Agency. Metribuzin was found not to produce a dermal sensitization reaction in guinea pigs under conditions of the study. Because no positive control data were submitted to verify the test animal's ability to respond to sensitizing agents, the study was classified as supplementary and does not satisfy guideline requirements 81-6 for a dermal sensitization study. The study can be upgraded to guideline, however, if data obtained from periodic laboratory tests on the animal's ability to mount a hypersensitivity reaction are submitted by the registrant and reviewed as acceptable.

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Reviewed by: Walter J. Kozumbo, Ph.D. Walter J. Kozumbo 12-20-91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. YMI 12/20/91
Section I, Toxicology Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Sensitization Study/Guinea Pigs (81-6)
TOX.CHEM.NUMBERS:	033D
MRID NUMBER:	415551-01
TEST MATERIAL:	Metribuzin (DIC 1468 Technical)
STUDY NUMBER:	T 0030584
TESTING FACILITY:	BAYER AG Fachbereich Toxikologik Institute of Toxicology/Agriculture Friedrich-Ebert-Strasse 217-333 D-56 Wuppertal 1 Federal Republic of Germany
SPONSOR:	BAYER AG Mobay Corporation Federal Republic of Germany
TITLE OF REPORT:	Study of Skin Sensitization Effect on Guinea Pigs
AUTHORS:	L. Diesing
REPORT ISSUED:	September 18, 1989
CONCLUSIONS:	When tested by the Buehler method, DIC 1468 (Metribuzin) produced no dermal sensitization reaction in guinea pigs. To validate this null response, however, some data should have been provided indicating that these animals respond to known skin sensitizers. Since concurrent positive controls were not performed, data obtained from routine laboratory checks of the test animal's capacity to mount a hypersensitivity reaction may be substituted.
CORE CLASSIFICATION:	Supplementary (Can be upgraded to guideline upon the acceptable review of requested information.)

I. MATERIALS

A. Test Material:

Metribuzin or DIC 1468 Technical is a solid white powder having a molecular weight of 214.3 and an empirical formula of $C_8H_{14}N_4OS$. Its chemical name is 4-amino-6-(1,1-dimethylethyl)-3-(methylthio)-1,2,4-triazin-5(4H)-one. It was used in this study at 93.5 % purity (batch no. 238603171). Metribuzin was formulated with 2% (v/v) Cremophor EL in physiological saline as a 50 % suspension (w/v). Formulation was continuously mixed with magnetic stirrer during application to maintain homogeneity.

B. Test Animals, Housing and Acclimation.

The test animals were young (5 to 7 weeks old), healthy SPF-bred guinea pigs of the strain DHPW, weighing between 277 and 369 g at the start of the study. The breeder was Winkelmann, in Borchen, Paderborn district, FRG. They were periodically tested by BAYER AG to validate their sensitivity response. All animals were kept in one room which was cleaned and disinfected once a month. The guinea pigs were fed (Altromin® 3022 maintenance diet for guinea pigs) and provided drinking quality tap water ad litbitum, and housed 5/cage during an acclimation period of at least 7 days, and 4/cage during the study. The animal room was environmentally controlled for temperature (22 ± 2 °C), humidity (at approximately 50 %), and light (a 12 h light/dark cycle).

II. METHODS

In a dose range-finding study, five females were used to select topical doses for induction and challenge that were non-irritating. From this range-finding study, it was determined that the induction and challenge doses would each consist of a 50 % suspension (w/v) of test article in a solution of 2 % Cremophor EL in physiological saline (v/v).

The dermal sensitization study on metribuzin was performed according to the Buehler Test methodology. Animals were randomly separated into 3 groups of 12, two negative control groups and one test group, that were each to receive serially 3 induction doses on days 0, 7, and 14, followed by one challenge dose on day 28. A second negative control group was used in case a second challenge was necessary. A positive concurrent control group was omitted in this study as the laboratory claims to check the sensitivity of guinea pigs at "regular time intervals" and to file the results. For the control groups, the induction doses consisted of vehicle alone (a 2% Cremophor EL saline solution); for the test group, they consisted of a 50 % test compound in vehicle. The induction

doses were applied by placing a hypoallergenic patch saturated with 0.5 ml volume of test suspension (or vehicle) to the pre-shaved, left flanks of the animals for 6 h. The challenge doses of test compound were similarly applied to the same flank area of both the test group and control group 1. In addition to these challenge doses of test compound, vehicle was applied as controls to the pre-shaved right flanks on challenge day 28. After treatment, compound residues were washed gently with physiological saline solution and depilated with Pilca-Creme (OLIVIN GmbH, Hamburg, FRG).

The guinea pigs were examined for signs of dermal redness 24 h after each induction and 24, 48 and 72 h after the challenge. Dermal redness was scored on a scale ranging from 0 (no reaction) to 3 (intense redness). At least once a day the guinea pigs were observed for signs of toxicity. Animals were weighed at the beginning and end of study.

III. RESULTS

The Buehler Test was used to test metribuzin for its dermal sensitization properties. In this study, neither the negative controls nor the test article caused any dermal irritation following the application of induction or challenge doses to young male guinea pigs (see attached pp. 21 & 22). In view of the fact that concurrent positive controls are recommended normally by the Buehler test method and that none of the test animals demonstrated even the slightest signs of irritation, the ability of these animals to respond to known sensitizers, such as 2,4-dichloronitrobenzene (DCNB), is warranted. In lieu of omitted concurrent positive controls, the laboratory may use archival information obtained from routine checks of the animals' capacity to respond to known sensitizers. The information should be from a test performed nearest to the date at which this study was initiated (February 28, 1989).

No signs of toxicity were observed during this study, and there was no substantial difference in weights between control and treated groups at the beginning or end of the study.

QA/GLP statements were affixed to the study.

IV. CONCLUSIONS

When tested by the Buehler method, DIC 1468 (Metribuzin) produced no dermal sensitization reaction in guinea pigs. To validate this null response, however, some data should have been provided indicating that these animals respond to known sensitizers. Since concurrent positive controls were not performed, data obtained from routine laboratory checks of the test animal's capacity to mount a hypersensitivity reaction may be substituted.

V. CORE CLASSIFICATION: Supplementary (Can be upgraded to guideline upon the acceptable review of requested information.)

METRIBUZIN

Page_____ is not included in this copy.

Pages 1 through 8 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

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